Обзоры

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Brain-gut axis: From the conditioned reflex to the microbiota-gut-brain communication system

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Abstract. Communication between the central nervous system (CNS) and the gastrointestinal tract is called the brain-gut axis. This communication network includes the CNS, hypothalamic-pituitary-adrenal axis, the autonomic nervous system (sympathetic and parasympathetic), the enteric nervous system and the gut microbiota. From the conditioned reflex activity in gastric acid secretion discovered by Pavlov to the recognition of the role of CNS in stress-induced gastric ulcer and exacerbation of intestinal inflammation, all these facts confirm the significance of brain-gut axis. Moreover, mental illnesses and depression also result in high risk for developing subsequent gastrointestinal mucosal injury. The brain-gut axis is bidirectional; therefore, not only the CNS affects the gastrointestinal functions, but the gut information is also forwarded to the CNS, which may modify its activity. Several observations suggested that changes in microbiome composition can be manifested in alterations of behavior and cognition; and a strong correlation between dysbiosis and psychiatric disorders has been observed. These observations substantially contributed to the establishment of the concept of the microbiota-gut-brain axis. The present work aims to overview the mutual role of brain-gut-microbiota and microbiota-gut-brain axis in the development of gastrointestinal and mental disorders as well as their mechanisms.

Keywords: brain-gut, gut-brain axis, microbiomes, stress, mental disorders, gastric ulceration, inflammatory bowel disease (IBD).

Introduction

The role of central nervous system (CNS) in regulation of gastrointestinal functions under physiological and pathological conditions has been in the focus of research for decades. Several data indicate that the brain-gut axis is bidirectional and the peripheral alterations in GI tract may influence the brain activity and functions. This bidirectional communication network, the brain-gut and the gut-brain axis, includes the CNS, the hypothalamic-pituitary-adrenal axis (HPA axis), the autonomic nervous system (sympathetic and parasympathetic), the enteric nervous system (ENS) and the gut microbiome. Therefore, this bidirectional communication system can be better characterised as the microbiome-gut-brain and brain-gut-microbiome axis.

Historical background of brain-gut axis

The role of the CNS in regulation of gastrointestinal function was first demonstrated in the 19th century by I. P. Pavlov in a brilliant experimental series on dogs. Among other fascinating findings, Pavlov was the first to demonstrate that animals could be conditioned to salivate when they hear a certain sound. Similarly, gastric acid and pancreatic secretions could be induced by smell and sight of food (cephalic phase of digestion). He also demonstrated that gastric acid secretion in fasted dogs starts almost immediately following exposure to appetising food without food actually entering the stomach (sham feeding) (Pavlov, Thompson 1902). He investigated the entire neural control of gastric secretion and the role of vagal nerves in this process, since the sham-feeding-induced gastric acid secretion was abolished by vagotomy.

Based on these findings, Pavlov was the first to demonstrate and systematically analyse the communication between the brain and the gastric function; thus he established the concept of brain-gut axis, which became one of the most exciting research topics in the next centuries. In 1904,

he was awarded Nobel Prize for achievements in gastroenterology. The significance of his findings continue to be recognised and cited also in the 20th and 21st century (Filaretova, Bagaeva 2016; Konturek et al. 2005; Smith 2000).

In the 20th century Hans Selye, who has been recognized as the father of stress research, introduced the concept of stress in a medical context. His theories on the responses of the organism to emotion, illness and injury helped to understand the causes and mechanisms of disease. According to his definition, stress is a non-specific response of the body (Szabo et al. 2012). His research on stress-related disorders, mechanisms and hormonal background, particularly in gastrointestinal tract, significantly contributed to and confirmed the concept of brain gut axis. He suggested that not only catecholamines released from the adrenal medulla (as Cannon concluded), but also glucocorticoids produced by adrenal cortex under the influence of ACTH play a crucial role in stress. Thus, Selye was the first to demonstrate the determining role of the hypophysis-adrenal cortex axis in the stress response (Selye 1936). He showed that experimental stress induced powerful gastric mucosal injury in rats and recognised the development of stress-related ulcers in humans, based on clinical reports on the dramatic increase of the number of perforated gastric and duodenal ulcers during bombings of London in World War II (Selye 1943).

Brain gut, gut-brain axis

Within the brain-gut axis, the brain-stomach axis represents a separate research area. Therefore, the brain-stomach axis is discussed separately.

Brain-stomach axis

The concept of Selye was confirmed by further clinical observations. Parallel with Selye, the role of CNS in development of peptic ulcer was suggested by Cushing who recognized that brain injury, cerebral stroke or tumor were associated with gastric mucosal damage (Cushing 1932). Furthermore, a significant association was found between schizophrenia and lower incidence for duodenal (but not for gastrojejunal) ulcers (Ozdemir et al. 2007). Different mental illnesses (like anxiety, panic disorder, panic attacks, and social phobia) resulted in high risk for developing subsequent peptic ulcer disease. Similarly, patients suffering from bipolar disorders exhibited a substantially higher risk of ulcer disease (Goodwin et al. 2013).

The mechanism of stress-induced gastric mucosal injury, bleeding and ulceration are probably associated with the release of adrenaline, noradrenaline from adrenal medulla resulting in redistribution of circulation to ensure the blood supply of vital organs, however, at the same time, the blood flow of visceral system, including the gastric mucosa, decreases. The decreased gastric mucosal microcirculation results in mucosal ischemia, and consequently, mucosal injury (Abdel-Salam et al. 2001; Monnig, Prittie 2011) (Fig. 1).

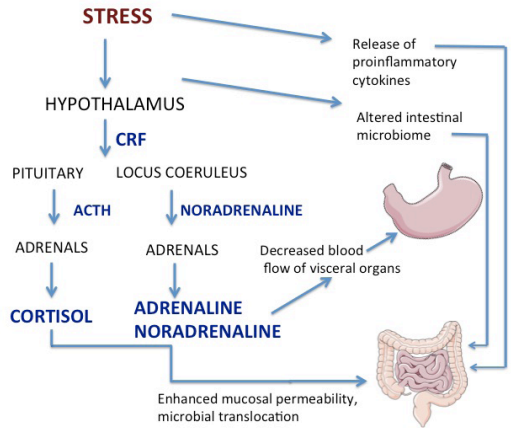

Fig. 1. The mechanism of stress-induced gastrointestinal mucosal injury. In stress adrenaline and noradrenaline are released from adrenals. Through circulation redistribution, the catecholamines gastric mucosal microcirculation and induce mucosal ischemia. The intestinal lesions may be associated with the release of proinflammatory cytokines, alteration of microbiome compostion as well as enhanced intestinal mucosal permeability and the consequent microbial translocation into intestinal wall

Beside the human data, experimental evidence confirmed the key role of brain-gut axis and provided further details for the mechanism. In these experiments, the compounds, mainly neuropeptides, were given centrally, intracerebroventricularly (icv.), intracistrenally (ic.) or into discrete brain areas to rats or mice and their effect on gastrointestinal functions (gastric mucosal lesions, acid secretion and motility) was determined.

Thyrotropin-releasing hormone (TRH), plays a key role in the regulation of the autonomic nervous system; it was among the first neuropeptides that was shown to inhibit the gastric mucosal injury induced by ethanol injected ic. or into the dorsal motor nucleus of vagus (DMN) in low (0.5–1.5 ng), non-secretory doses (Tache 2012). This finding was followed by an intensive research, and several neuropeptides were shown to be gastroprotective if given centrally, such as peptide YY (PYY) (ic.), amylin (icv.) (both of them are involved in regulation of food intake), α-calcitonin gene-related peptide (α-CGRP) (ic.), adrenomedullin (ic.) (Tache 2012). The same group also showed that

corticotropine releasing factor (CRF), having outstanding role in initiation of stress response, exerted mucosal protective effect injected icv. against cold-restrain stress induced mucosal lesions and reduced C-fos expression in DMN (Wang et al. 1996). This finding might suggest that during the development of stress-related gastric mucosal injury, compensatory mechanisms are also activated to attenuate the deleterious effect of stress.

Furthermore, opioid peptides with different selectivity to the opioid receptor types such as the non-selecive β-endorphin (released also in stress response), the δ-opioid receptor selective [D-Ala(2),D-Leu(5)]-enkephalin (DADLE), [D-Pen(2),D-Pen(5)]-enkephalin (DPDPE) and deltorphin II as well as μ-opioid receptor selective Ala(2),Phe(4),Gly(5)-ol]-enkephalin (DAGO) were shown to exert powerful gastroprotective effect in low, non-analgesic doses. Endomorphins (endomorphin I and endomorphin II), highly selective μ-opioid receptor agonists, discovered in 1997 (Zadina et al. 1997) differ in basic structure from the above mentioned opioid peptides (β-endorphin, enkephalins and deltorphin), since they are tetrapeptides. They are widely distributed in the CNS. Endomorphins proved to be particularly potent; they caused a significant inhibition of ethanol-induced lesions in fentomolar doses (given icv.). In addition, elevation of brain level of endomorphins via inhibition of their degradation by diprotin A, a dipeptidyl peptidase IV inhibitor, also resulted in a gastroprotective effect. This finding might have practical benefit. Namely, peptides do not cross the blood-brain barrier following peripheral administration (unless they have special transporter), therefore, their potential therapeutic application is very limited. However, if elevation of their endogenous level by inhibiting their degradation results in the same beneficial action as the centrally injected peptide itself, it may be considered whether this pharmacological approach might be utilized in the drug development strategy (Gyires, Rónai 2001; Gyires et al. 2013; Gyires, Zádori 2014).

Moreover, the group of peptides that have a key role in regulation of food intake, also exert mucosal protective action, indicating that they might play a role in gastric mucosal defensive processes as well. PYY and amylin were mentioned above. Furthermore, ghrelin (icv., ischemia-reperfusion model), orexin-A (ic., ethanol-model), leptin (icv., ethanol and ischemia-reperfusion) and nesfatin-1 (icv., ethanol) reduced the mucosal lesions in different ulcer model (Gyires, Zádori 2014).

The effective gastroprotective dose range of neuropeptides varies widely from fmol/rat (endomophin, β-endorphin) to nmol/rat (ghrelin, orexin, deltorphin II) given icv., ic. or into discrete brain areas (Gyires, Zádori 2014).

How is the centrally-induced gastroprotective effect conveyed to the periphery?

Pavlov already demonstrated the role of vagal nerve in the gastric acid secretion and salivation in sham feeding and conditional reflex in dogs. Similarly, the dorsal vagal complex and vagal efferents were shown to play a crucial role in conveying the centrally initiated effect to the periphery, and the vagally mediated gastroprotective effect has been demonstrated for the majority of neuropeptides. First, the mucosal protective effect of TRH, or its stable analogue RX-77368, injected ic. or into or the dorsal motor nucleus of vagus was shown to be abolished by both vagotomy and atropine indicating the involvement of vagal cholinergic pathways in the centrally initiated gastroprotective effect. Activation of vagal cholinergic pathways stimulates the gastric mucosal nitric oxide and prostaglandin release as well as the effector function of capsaicin-sensitive afferent fibers which is manifested in calcitonin gene-related peptide (CGRP) release (Tache 2012; Gyires, Zádori 2014; Gyires et al. 2013; Holzer et al. 1990).

However, beside vagal nerve, other mechanisms have also been identified. For example, the gastroprotective effect of centrally injected ghrelin could be blocked only by parallel inhibition of both cholinergic and adrenergic systems, indicating that both systems are likely to be involved in the mucosal protective effect of centrally injected ghrelin (Pawlik et al. 2011). Similarly, both adrenergic and cholinergic systems also play a role in the gastroprotective effect of nociceptin (N/OFQ) given either centrally (icv.) or peripherally (intaperitoneally), since its protective action was inhibited by vagotomy or atropine as well as bretilium (Polidori et al. 2005). However, the gastroprotective effect of angiotensin II injected into the paraventricular nucleus of the hypothalamus was not influenced by vagotomy or atropine, but was blocked by propranolol or disconnection of the nerves innervating the adrenal glands, indicating the role of the sympathetic-adrenal gland/beta adrenoceptor pathway (Zhang et al. 2008).

Brain-gut axis

The most common chronic and relapsing inflammatory condition of the intestinal tract is the inflammatory bowel disease (IBD): Crohn's disease (CD) and ulcerative colitis (UC). Both diseases have immunological background and increasing number of evidence suggests that crosstalk between the nervous and immune systems may have a significant influence

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on the regulation of the immune response and, consequently, the inflammatory processes.

Depression and IBD

Several data indicated that IBD may coexist with mental disorders and the occurrence of different mental diseases, stress, major depression and anxiety are more frequent in IBD patients than in the control population (Kurina et al. 2001; Filipovic, Filipovic 2014). In addition, IBD can exacerbate in the presence of psychiatric disorders. Major depression can also be responsible for the failure of the successful treatment of IBD with infliximab. Therefore, identification and management of major depressive disorders should be part of the clinical treatment (Persoons et al. 2005).

Why can depression aggravate or even cause IBD?

Intensive research has been focused to clarify how nervous system may influence the immune system. It was found that in the GI tract, vagal innervation plays a basic role in controlling intestinal immune activation. Namely, the release of acetylcholine reduces the immune cell activation by interacting with α-7 nicotinic acetylcholine receptors (Matteoli, Boeckxstaens 2013). It has been demonstrated that depression results in impaired parasympathomimetic functions and, consequently, the activation of inflammatory processes (see review: Bonaz et al. 2018). For example, in patients with depression the inflammatory parameters, like C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α) increased, similarly the leukocytes counts were also higher. Antidepressant treatment resulted in a decreased level of TNF-α, CRP, and leukocyte counts (Tuglu et al. 2003) (Fig. 2).

Experimental results are in line with the human findings. Increased gut inflammation, disease activity index, myeloperoxidase activity, elevated colonic tissue levels of interleukin-1β (IL-1β), interleukin-6 (IL-6) and TNF-α were observed in vagotomised mice with dextran sulfate sodium (DSS) and hapten-induced colitis compared to sham-operated mice administered DSS or hapten. It was concluded that the vagus nerve plays an inhibitory role on inflammatory parameters in acute colitis and identification of counter-inflammatory neuronal pathway might represent a new therapeutic target for treating acute exacerbations of inflammatory bowel disease (Ghia et al. 2006; 2008).

Furthermore, reactivation of chronic colitis induced by dextran sulfate sodium (mimics UC), was observed in vagotomised mice or in mice with experimental depression elicited by icv. infusion of reserpine, this effect was reversed by the treatment with antidepressant, desmethylimipramine (DMI). Macrophages isolated from mice exposed to vagotomy or experimental depression resulted in a selective increase of pro-inflammatory cytokine release, this effect was reversed by DMI. These findings suggest the critical role of macrophage in the reactivation of chronic colitis by depression or vagotomy (Ghia et al. 2011).

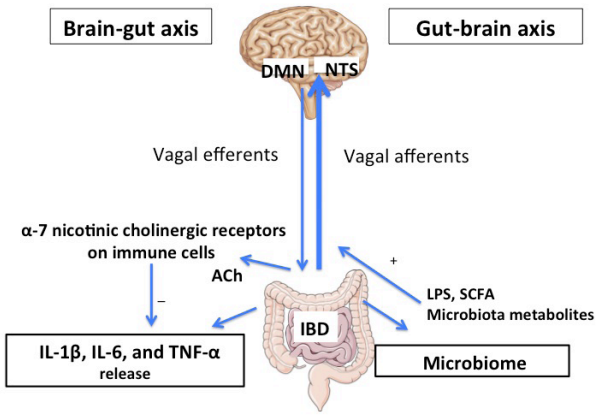

Fig. 2. The role of vagal nerve in brain-gut and gut-brain axis. The release of acetylcholine from the nerve terminal of efferent fibers reduces the immune cell activation by interacting with α-7 nicotinic acetylcholine receptors. In depression, impaired parasympathomimetic functions can be observed, resulting in activation of inflammatory processes. Afferent fibers of vagal nerve are able to sense the microbiota through microbiota derived compounds, metabolites such as lipopolysaccharide (LPS) and sort chain fatty acids (SCFAs), and transfer this gut information to the brain through nucleus tractus solitarii (NTS), part of dorsal vagal complex

Stress and IBD

In humans, psychosocial factors may influence the course of IBD. Adverse life events and chronic stress can contribute to disease relapse. Moreover, experimental stress can increase mucosal inflammation both in patients with IBD and in animal models of colitis. Although increasing number of findings suggest the pro-inflammatory effects of stress in IBD, very few studies have identified stress reduction as a therapeutic possibility (Mawdsley, Rampton 2006). Bonaz and Bernstein (2013) emphasised the psychophysiological vulnerability of patients with IBD, for example mood disorders, distress or increased perceived stress. Since multiple evidence indicates that stress or other negative psychological factors may have a deleterious effect on the course of the disease, patients with IBD may need psychotherapy.

Why does stress produce a negative impact on the course of IBD?

Several mechanisms have been identified.

- Disruption of intestinal mucosal tight junctions by acute and chronic stress was observed. Namely, increase in serum corticosterone in chronic stress was found to induce a decrease in specific intestinal epithelial tight junction proteins (Zheng et al. 2017). This can lead to enhanced mucosal permeability of the colon, and, consequently, microbial translocation into the intestinal wall. The increased number of bacteria in the colonic tissue provokes an excessive release of cytokine and a consequent inflammation.
- Acute minor stress is accompanied by activation of hypothalamus-pituitary axis, that results in a prompt increase in cortisol and catecolamine levels (Koob 1999) as well as the concentration of pro-inflammatory cytokines such as TNF- α, interleukin-8 (IL-8), IL-1β and IL-6. Thus, acute stress is characterized by enhancement of immune function (Brzozowski et al. 2016). In contrast, chronic sustained stress induces a prolonged increase of cortisol for several days in humans, which may result in immunosuppressive action (Straub et al. 2005) (Fig.1).
- Change of composition of microflora is considered to be one of the main mechanisms in the pathogenesis of IBD. Stress may alter the intestinal microbiomes. For example, under ex vivo condition, dopamine and noradrenaline increased enterohemorrhagic *E. coli* O157:H7 adherence in murine cecum compared to untreated control group. These findings suggest that conditions associated with elevated catecholamine release, such as stress exposure, may influence host susceptibility to E. coli O157:H7 infection (Chen et al. 2003). Furthermore, stress may affect microbial populations, including the lactobacilli, in mice, which have beneficial effect in human intestinal homeostasis. The stress-induced reduction of their population could initiate pathological alterations (Galley et al. 2014). Recently, there was an experimental series aimed to explore how gut microbiota changes in adolescent rats that were exposed to fixed period of restraint stress. It was found that while adolescent chronic stress-induced differences in microbial species and distribution disappeared three weeks after the stress treatment, the differences in microbial metabolic profiles could also be observed in adulthood (Xu et al. 2020) (Fig. 1).

Gut-brain axis

As mentioned in Introduction, the brain-gut axis is bidirectional; numerous experimental data suggested a complex interaction between the GI tract and the CNS, that confirms the importance of gut-brain axis. Convincing evidence from both human and animal studies show that inflammatory processes in the gut may trigger central changes that result in altered brain function.

On the other hand, recently, the importance of gut microbiota in these interactions has been recognized. Namely, the cells of the gastrointestinal tract are also under the influence of the gut microbiota. Several human and experimental data indicate that microbiome plays an important role in the gut-brain axis, and therefore the concept of microbiome-gut-brain axis has been introduced (Carabotti et al. 2015).

IBD and CNS disorders

The significance of gut brain axis is supported by multiple clinical data. There is growing evidence that IBD is associated with anxiety- and depression-related disorders, which contribute to the social burden of these diseases. Comorbidity of psychological/psychiatric disorders and IBD often can be observed, and when they coexist it influences the course of both diseases. IBD impairs the quality of life of the patients not only because of the intestinal (abdominal pain associated with diarrhea, rectal bleeding, and malnutrition) and extraintestinal (e.g. fever, weight loss, arthritis, arthralgia, mucocutaneous, ophthalmologic lesions) symptoms, but also because of the impaired mental health (Holzer et al. 2015).

Recently, aberrant brain activity in patients with mildly to moderately active UC has been shown by resting state — fMRI study. Their study revealed alterations in the limbic system that might play an important role in cognitive impairments in patients with active UC (Fan et al. 2019).

Furthermore, intestinal inflammation can induce mood disorders, alteration of circadian rhythm and changes in appetite. Preclinical studies demonstrated that effective treatment of intestinal inflammation improves the associated behavioural impairment. Therefore, a holistic approach to the treatment of patients with IBD and appropriate management of behavioural disorders are necessary (Collins 2020).

Convincing evidence was provided by Canadian researchers. They found 21.2% and 25.8%, rate of anxiety and depression, respectively, in patients with IBD, in contrast with the general Canadian population. In an earlier Canadian study, IBD patients demonstrated 4.7% and 11.3% 12-month and lifetime depression rates, respectively, while their

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12-month and lifetime Generalised Anxiety Disorder rates were 2.6% and 8.7%, respectively (Byrne et al. 2017).

In addition, not only in GI tract, but in any peripheral organ, inflammation may induce a common pattern of CNS response, the so-called "sickness syndrome", which includes fever, sleepiness, anorexia, hyperalgesia, fatigue, mood alterations, cognitive dysfunction and corticosteroid release (Saper et al. 2012).

Human observations have been confirmed by experimental findings. For example, dextran sulphate sodium induced colitis in mice affected their stress-associated behavior; prolonged immobility during the water avoidance stress session was observed, parallel with brain region-dependent alterations of neuropeptide Y (NPY), NPY receptor Y1, CRH, CRH receptor 1, brain-derived neurotrophic factor and glucocorticoid receptor gene expression (Reichmann et al. 2015).

Similarly, experimental colitis elicited by dextran sodium sulphate in mice was shown to induce CNS excitability in response to kainic acid and increased anxiety-related behaviour as revealed using the elevated plus-maze and open field models (Nyuyki et al. 2018). Furthermore, peripheral inflammation through administration of TNF-α to mice, was shown to activate the brain microglia and elevate pro-inflammatory factors, as well as delayed and progressive loss of dopaminergic neurons in substantia nigra characteristic in Parkinson's disease (Qin et al. 2007).

Why can intestinal inflammation induce brain alterations?

Several mechanisms have been identified as responsible for the gut-CNS communication. For example, it is well known, that cytokines, (IL-1β, IL-6, and TNF-α) play a pathogenic role in IBD and also appear in the circulation (Nikolaus et al. 1998). These cytokines also play a role in the pathogenic mechanisms of several psychiatric diseases associated with inflammation, like behaviour-disorders, cognitive changes and affective disorders, since cytokines may alter neurotransmission in the brain (Dantzer 2009).

Cytokines circulating in the blood affect CNS function through a variety of pathways, since these cytokines are too bulky to cross the blood-brain barrier (BBB) in large amounts.

- It was shown that in minor amounts they can be actively transported (Banks, Erickson 2010). Their transport rates differ depending on cytokines, brain regions, physiological circumstances and diseases (Banks 2005).
- Another mechanism by which cytokine can affect brain function is that cytokines — through their receptors located at BBB on perivascular and endothelial cells — can increase the expression of cyclo-oxygenase-2 (COX-2) and biosynthesis of PGE_2 (Schiltz, Sawchenko 2002), and prostaglandins are probably a key mediator responsible for brain responses to systemic inflammation by their ability to cross the BBB (Saper et al. 2012).
- Additional mechanism how peripheral inflammation may signal to CNS is the neural pathway when cytokines sensitise and/or stimulate vagal and spinal afferent neurons and thus contribute to a rapid propagation of immune signals (Holzer et al. 2015).
- Finally, the signalling mechanisms from the periphery result in additional synthesis of cytokines inside the brain, such as IL-1, IL-6, and TNF-α, most probably by activating the microglial cells (Dantzer 2009; Beynon, Walker 2012).

Microbiome-gut-brain axis

The most important components of gut-brain-axis are the CNS, the ENS system and the intestinal microbiota (Ambrosini et al. 2019).

IBDs are complex diseases caused by interaction of environmental, genetic factors, immune dysregulations, barrier dysfunction, and changes in microbial flora. Under normal physiologic condition, the intestinal barrier prevents the invasion of microbes and toxins into the mucosa.

Several observations suggested that changes in microbiome composition can be manifested in alterations of behavior and cognition, substantially contributing to the establishment of the microbiota-gut-brain axis as a concept (Holzer et al. 2015; Stilling et al. 2014).

Approximately 75% of intestinal microbioms belong to *Firmicutes, Bacteroidetes Firmicutes* and *Bacteroidetes* phyla (Eckburg et al. 2005). It has been recognised that the presence of a healthy and diverse gut microbiota is important for the normal cognitive and emotional development. A newborn is first exposed to the mother's vaginal microbiota which is important in the offspring's microbial colonisation and it was demonstrated that the gut microbiota has a central role in the development and maturation of the human CNS and ENS in these early postnatal weeks (Mueller et al. 2015). This process can be influenced by several factors, including the Cesarean section, perinatal antibiotics and formula feeding that may correlate with increased risks of metabolic and immune diseases. For example, following Cesarean section the risk of celiac disease, asthma, type 1 diabetes, and

obesity may increase in the offspring. Similarly, the treatment with antibiotics during pregnancy may increase the prevalence of obesity and asthma in childhood (Mueller et al. 2015).

Furthermore, several data show a strong correlation between dysbiosis and psychiatric disorders, autoimmune disorders, irritable bowel syndrome (IBS), IBD and obesity (Wang, Kasper 2014).

Autism is a developmental neuro-behavioral disorder. Although the possible role of gut microorganisms in the pathogenesis of autism is controversial (Mangiola et al. 2016), it was found that large amount (10 times more) of species in the Clostridium genus was identified in the fecal samples of autistic children (Parracho et al. 2005). Furthermore, the gut barrier alteration may also contribute to autism (Emanuele et al. 2010).

Information of the microbiota-gut-brain communication axis can be conveyed from the gut to the brain by several mechanisms, such as:

- Vagal and spinal afferents. Microbial factors, such as polysaccharides or sort chain fatty acids can stimulate vagal afferents (Mao 2013). They carry feedback from the intestine to the brain stem, hypothalamus and limbic system where it is integrated, and then generate an adapted or inappropriate response (Eisenstein 2016; Bonaz et al. 2018). Vice versa, descending pathways from the limbic system also influence the function of the gut.
- Immune mediators, gut hormone- and gut microbiota derived molecules. The bacterial products may stimulate enteroendocrine cells resulting in the release of several neuropeptides (like PYY, NPY, cholecystokinin, glucagon-like peptide-1 and -2, and substance P). These neuropeptides entering the circulation may directly influence the enteric nervous system (Holzer, Farzi 2014; Holzer et al. 2015).
- Neuroactive substances produced by microbiome, such as catecholamines, histamine, and other compounds can influence the host neurophysiology and neurotransmission in the GI tract by binding to their receptors. In addition, after absorption these substances can enter the systemic circulation where they can induce receptor-mediated actions.
- Increased intestinal permeability. Toxins produced by intestinal pathogenic microorganisms and the focal inflammation induced by immune responses developed against these pathogens can increase gut permeability (Lyte 2013).
- The non-specific factors such as lipopolysaccharide (LPS) can activate Toll-like receptor 4 (TLR4) on microglial cells which can provoke the release of inflammatory cytokines within the CNS (Kim et al. 2012) (Fig. 2).

Summary and conclusion

There is a bidirectional communication and interaction between the brain and the gut. The brain regulates the gut microenvironment and microbiota composition, while the gut can modulate the brain function. Within the brain-gut axis, the brain-stomach axis should be discussed separately.

The brain-stomach axis has prominent role in the pathogenesis of stress ulcer. The decrease of gastric mucosal protective mechanisms and reduced gastric mucosal blood flow may be the dominant mechanisms responsible for the development of stress-induced gastric mucosal injury, ulceration. Beside stress, anxiety, panic disorder, panic attacks, social phobia as well as bipolar disorders exhibited a substantially higher risk for gastric ulcer disease.

Much less is known about the impact of *stomach-brain axis*. It has been observed that exposure of gastric mucosa to different irritants resulted in a rapid expression of c-Fos mRNA in nucleus of the solitarii tract (NTS), area postrema of the brainstem (Schuligoi et al. 1998). However, whether the c-Fos expression correlates with any functional mechanism has not yet been clarified.

On the contrary, increasing number of evidence suggests the importance of *brain-gut* axis; namely, the crosstalk between the central nervous and immune systems may have a significant influence on inflammatory processes. Stress and pre-existing behavioural illnesses, such as depression, result in increased susceptibility to inflammatory stimuli and can provoke and reactivate intestinal inflammatory processes, like IBD. The increased risk of intestinal inflammation in stress is likely to be associated with increased intestinal permeability and the consequent translocation of bacteria, the increased level of proinflammatory cytokines as well as changes in composition of intestinal bacterial flora. Multiple data indicate that IBD may coexist with mental disorders; major depression and anxiety are more frequent in IBD patients than in the control population. Depression is characterised by an impaired parasympathomimetic functions and consequently inflammatory processes are activated. Namely, cholinergic system via α-7 nicotinic acetylcholine receptors reduces the immune cell activation and the release of pro-inflmmatory cytokines.

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Vice versa, preclinical and clinical observations suggest that intestinal inflammation alters brain functions, confirming the importance of *gut-brain axis.* There is growing evidence that IBD is associated with anxiety- and depression-related disorders. Also, comorbidity of psychological/psychiatric diseases and IBD can often be observed, and when these diseases coexist, they influence the course of each other.

The significance of *microbiota-gut-brain axis* communication system has been suggested recently by the observations that changes in microbiome composition can be manifested in alterations of behavior and cognition. Strong correlation was found between dysbiosis and development of psychiatric disorders.

This complex communication network requires a holistic approach to the management of patients with IBD, as well as monitoring and treating the behavioural disorders. Well-designed clinical studies on antidepressants are highly needed to evaluate their effect on the inflammatory disease activity (Collins 2020).

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